UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

DATE: June 21, 2000

MEMORANDUM

SUBJECT: ***1,4-Bis(bromoacetoxy)-2-butene*** : Toxicology Review for the Reregistration Eligibility Decision (RED) Document.
PC Code: 035605 **DC Bar Code:** D251929

FROM: Jonathan Chen, Ph.D.
Toxicologist, Risk Assessment and Science Support Branch (RASSB)
Antimicrobial Division (7510C)

THROUGH: Allen Vaughan
Team Leader, Team Three
RASSB / AD

And

Norm Cook
Chief
RASSB / AD

TO: Julie Fairfax
Product Manager, Team #36
Regulatory Management Branch II / AD

Attached is the revised Hazard Assessment of 1,4-Bis(bromoacetoxy)-2-butene **(BBAB)** for purposes of issuing a Registration Eligibility Decision (RED) Document for this chemical.

June 21, 2000

1,4-Bis(bromoacetoxy)-2-butene

(BBAB)

PC Code: 035605

Evaluation of Toxicology Database for the Reregistration Eligibility Decision Document Disciplinary Chapter

Date completed: June 20, 2000

Prepared for:

Regulatory Management Branch II
Antimicrobial Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Arlington, VA 22202

Prepared by:

Jonathan Chen, Ph.D.
Risk Assessment and Science Branch
Antimicrobial Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Arlington, VA 22202

TABLE OF CONTENTS

0.0 BACKGROUND

The chemical 1,4-Bis(bromoacetoxy)-2-butene (**BBAB**) is currently produced and manufactured by Buckman Laboratories, Inc.[1] as a slimicide**.** On October 16, 1995, Buckman Laboratories International, Inc. registered the technical grade use of this product (EPA Registration NO. 1448-374). According to information provided by the registrant, all **BBAB** produced is currently registered for the following usages:

1. Oil field injection water and other field water systems to control slime forming bacteria (as a slimicide);

2. Water-based coatings as a preservative to inhibit bacterial and fungal growth; and

3. Pulp and paper mills as a slimicide in paper machines or in the preservation of paper coating formulations/chemicals.

In addition to the non-food use scenarios (See Human Exposure RED Chapter), using **BBAB** in pulp and paper mills as a slimicide in paper machines or in the preservation of paper coating formulations/chemicals is considered an indirect food use. The Food and Drug Administration (FDA) has approved this use under 21 CFR 176.300, Slimicides. However, regulation of **BBAB** under Section 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) does not relieve the registrant of meeting the standard under Section 408 as amended by the Food Quality Protection Act (FQPA), when the active ingredient is subject to regulation as a food-use pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under Section 408, a determination of safety for residues of a pesticide that may be in food is required, and as defined in Section 408(b)(2)(ii),"that there is a reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residues, including all anticipated dietary exposures and all other exposures for which there is reliable information." Therefore, a dietary risk assessment under FQPA is necessary for **BBAB** to support the intended use in food-contact paper and paperboard.

To complete a risk assessment for an indirect food use chemical for which the FDA has established a food additive regulation that specifically states that the use is "safe", the Antimicrobials Division, OPP, has established a two-tiered system of toxicology data requirements. Tier I toxicology data requirements apply to all indirect food uses that result in residue concentrations ranging from 0-200ppb. The requirements consist of an acute toxicity testing battery, subchronic toxicity studies in both the rodent and non-rodent (with the inclusion of neurotoxicity testing endpoints in the rodent assay), a developmental toxicity study in the rat, a two-generation reproduction toxicity study in the rat, and a mutagenicity testing battery. The registrant may choose to combine the developmental and reproductive toxicity testing per FDA protocols, but if so, must first submit the protocol to the Agency for approval. Tier II studies would be triggered by the presence of significant (i.e. $200ppb) residues in food or evidence of significant toxicity from the Tier I data set, which may include developmental / reproductive, or other systemic toxicity such as presence of neoplastic growth or significant target organ toxicity. In such cases, chronic toxicity and carcinogenicity testing would be required.

1.0 HAZARD CHARACTERIZATION

BBAB is moderately acutely toxic by oral and dermal routes. There are no available acute inhalation, primary eye

---

[1] Buckman Laboratories, Inc. 1256 N. McLean Blvd, Memphis, TN 38108, USA. Telephone Number: (901)278-0330.

irritation, primary skin irritation or dermal sensitization studies. Due to the corrosive properties of **BBAB**, this chemical is classified as toxicity category I for potential acute inhalation toxicity, eye irritation, dermal irritation and dermal sensitization.

As indicated by the subchronic rat study (MRID 44757001), the primary target organ for oral exposure to **BBAB** is the stomach. In both sexes , at low-treatment dose, slightly increased incidence of minimal hyperkeratosis and hyperplasia of the nonglandular mucosa of the stomach were noticed. Mid- and high-dose animals had mild anemia (possibly due to blood loss from the stomach).

Two studies were submitted to evaluate the developmental toxic effects of **BBAB** (one range-finding study and one rat prenatal developmental toxicity study). Results of these two study indicate there was no evidence of developmental toxicity for **BBAB**, but the data are insufficient to make a full assessment.

Three mutagenicity studies were submitted to evaluate the mutagenic potential of **BBAB**. Although with microsomal activation, **BBAB** is moderately mutagenic in the mouse lymphoma assay, **BBAB** is negative in both the Ames test (with or without microsomal activation) and in the *in vivo* ICR Mouse Bone Marrow Micronucleus Test.

A complete dietary and FQPA risk assessment as well as an inhalation risk assessment for **BBAB** must be deferred, pending submission of the missing studies.

2.0 AVAILABLE DATABASE

As summarized in **Table 1**, eight studies were submitted by the registrant to characterize the toxicity of **BBAB.**

Table 1. TOXICOLOGY DATABASE FOR BBAB

Guideline Number	Test	Technical		
		Required	Satisfied	MRID Number
870.1100	Acute Oral Toxicity	Y	Y	431811-01
870.1200	Acute Dermal Toxicity	Y	Y	431524-01
870.5265	Reverse Gene Mutation - Ames Test	Y	Y	432010-01
870.5385	Bone Marrow Micronucleus Test	Y	Y	431563-01
870.5300	In vitro Mammalian Cell Gene Mutation Test	Y	Y	4320260-1
870.3700	Developmental toxicity - Range Finding	Y	Y	447394-1
870.3700	Developmental toxicity	Y	Y	4475090-1
870.3100	Subchronic Oral Toxicity	Y	Y	447570-01

Y - Yes; **N** - no

In this toxicology assessment chapter, the toxicology database of **BBAB** is evaluated, and the toxicological endpoints

used for risk assessment are selected. In addition, the data gaps in the database are also identified.

3.0 DATA GAP(S)

There are no guideline studies available for assessment of the inhalation toxicity, reproductive toxicity, or neurotoxicity of BBAB. In addition, for non-food uses of BBAB, the following toxicology data are required for adequate hazard and risk assessment:

1. A dermal penetration study (OPP Guideline 85-7, OPPTS Number 870-7600),
2. A 90-day dermal study (OPP Guideline 82-3, OPPTS Number 870-3250),
3. A 28-day inhalation study at one dose level, with 2.5%**BBAB**, (OPP Guideline 82-4, OPPTS Number 870-3465), and
4. An oral neurotoxicity screening battery study (OPP Guideline 81-8, OPPTS Number 870-6200).

Because use of **BBAB** in pulp and paper mills as a slimicide in paper machines or in the preservation of paper coating formulations/chemicals is considered an indirect food use, and as discussed in the **Background Section**, the following toxicity data are required depending on the level of anticipated residue:

If **BBAB** residues in food are greater than 200ppb, five additional studies are required:

1. A developmental toxicity study in rabbit (OPP Guideline 83-3, OPPTS Number 870-3700),
2. A two-generation reproductive toxicity study in rat (OPP Guideline 83-4, OPPTS Number 870-3800),
3. A chronic study in non-rodents (OPP Guideline 83-1, OPPTS Number 870-4100),
4. A combined chronic toxicity/carcinogenicity study in rat (OPP Guideline 83-5, OPPTS Number 870-4300), and
5. A carcinogenicity study in the mouse (OPP Guideline 83-2, OPPTS Number 870-4200).

If the registrant provides data that show **BBAB** residues in food are between 0- 200 ppb, only two additional studies are required:

1. A 90-day non-rodent study with the inclusion of neurotoxicity testing endpoints (OPP Guideline 82-1, OPPTS Number 870-3100); and
2. A two-generation reproductive toxicity study in rat (OPP Guideline 83-4, OPPTS Number 870-3800).

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

The acute toxicity data on **BBAB** technical is summarized below in **Table 2**. As summarized, the acute oral LD_{50} of **BBAB** was 292 mg/kg in male and 163 mg/kg in female Sprague-Dawley rats. Clinical signs of toxicity included decreased activity, salivation, wobbly gait, piloerection, diarrhea, urinary/fecal staining, hypothermia, rales and death. Necropsy findings included dark red thymus, mottled lungs, abnormal mucosa, and congested brain meninges.

The dermal LD_{50} for both male and female rabbits is greater than 2000mg/kg when applied to rabbit skin for 24

hours. Two animals died on study day 2. Clinical effects noted in survivors were fecal/urinary staining, soft stool, and dermal irritation at the test sites. Necropsy examination revealed gastric irritation and congested meningeal vessels in the brain.

Table 2: Acute Toxicity of 1,4-Bis(bromoacetoxy)-2-butene (BBAB)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	431811-01	LD_{50} = 292 mg/kg (**%**), 163 mg/kg (**&**), and 220mg/kg (combined)	II
81-2	Acute Dermal	431524-01	LD_{50} > 2000mg/kg	III
81-3	(1) Acute Inhalation	No Study available		I
81-4	(1) Primary Eye Irritation	No Study available		I
81-5	(1) Primary Skin Irritation	No Study available		I
81-6	(1) Dermal Sensitization	No Study available		I

Note:

(1). Acute inhalation, primary eye irritation, primary skin irritation and dermal sensitization studies were not conducted due to the corrosive properties of **BBAB**. For these endpoints, **BBAB** was classified as toxicity category I on the bases of its known corrosivity.

As shown, **BBAB** is moderately acutely toxic by oral and dermal routes. However, there are no available acute inhalation, primary eye irritation, primary skin irritation or dermal sensitization studies. Due to the corrosive properties of **BBAB**, this chemical is classified as toxicity category I on the basis of its known corrosivity.

4.2 Subchronic Toxicity

There is one 90-day rat gavage study (MRID 44757001) evaluating the non-acute toxicity of **BBAB**. In the study, 10 Sprague-Dawley Crl:CD®(SD)IGS BR rats/sex/group were administered **BBAB** (Lot No. KDD, Batch # 9, 93.1% a.i.) in Mazola® corn oil orally by gavage at doses of 0, 4.5, 22.5, or 39.1 mg/kg/day for a minimum of 90 consecutive days. An additional 10 animals/sex/group were incorporated into the control and high-dose groups for a recovery phase. For high-dose animals, the test article was initially administered at a dosage of 45 mg/kg/day on days 1-37, but was reduced to 35 mg/kg/day on days 38-91 due to dose-related toxicity, for a total time-weighted dose of 39.1 mg/kg/day.

Treatment with **BBAB** resulted in significant toxicity in mid- and high-dose animals. In the high-dose groups, 4/20 males and 3/20 females died or were euthanized moribund due to treatment-related toxicity. During the treatment period, clinical signs in mid- and high-dose animals included a dose-related increased incidence of salivation prior to and post dosing, and

high-dose males and females additionally exhibited decreased activity (11/20 and 3/20, respectively) and a wobbly gait (8/20 and 3/20, respectively). High-dose females had decreased mean absolute body weights at the end of treatment (day 90; 92% of controls; $p<0.05$). Reductions in mean body weight gains during treatment were biologically significant in high-dose males and females, with the greatest reduction occurring toward the end of treatment on days 57-90 (58% and 70% of controls, respectively, statistical analysis not conducted). Statistically significant decreases ($p<0.05$; 0.01) in food consumption in the high-dose males (82-93%) and females (80-90%) and mid-dose females (80-90%) may have been treatment-related.

Treatment with **BBAB** also resulted in irritative/corrosive effects on the stomach. Mid- and high-dose animals had mild anemia (possibly due to blood loss from the stomach) as indicated by generally statistically significant, dose-related decreases in erythrocytes, hemoglobin, and hematocrit. A regenerative response to the anemia in mid- and high-dose animals was evidenced by generally statistically significant increases in MCV and MCH, changes in red blood cell morphology that are consistent with immature erythrocytes (macrocytes, polychromasia, and anisocytosis), and minimal to moderate splenic extramedullary hematopoiesis observed during microscopic examination.

High-dose animals additionally had enlarged spleens and increased absolute and relative spleen weights (94 and 107% vs. the controls for males, respectively; 146 and 163% vs. the controls for females, respectively). Eroded and thickened areas of the stomachs of mid-and high-dose animals were observed during gross necropsy, while microscopic examination revealed multiple findings in the nonglandular mucosa of the stomach including edema, hemorrhage, inflammation, hyperkeratosis, and hyperplasia. Ulcers (high-dose) and erosion (mid- and high-dose) of the nonglandular epithelium were also sometimes present.

Low-dose males and females had a slightly increased incidence of minimal hyperkeratosis (3/10 for both) and hyperplasia (2/10 and 4/10, respectively) of the nonglandular mucosa of the stomach (controls: 0/10 for both lesions). In the female, minimal edema of the stomach and minimal extramedullary hematopoiesis were seen in 1/10 animals compared to 0/10 in the control group for both lesions.

Clinical chemistry analysis revealed statistically significantly elevated levels of serum chloride in mid- and high-dose males (+11% and +30%, respectively) and females (+9 and +15%, respectively). Microscopic evaluation of the liver revealed minimal to marked periportal hepatocyte vacuolation in 10/12 high-dose males, and minimal to mild vacuolation in 2/10 mid-dose males: no other supporting markers of liver toxicity were present.

Following the 28-day recovery phase, body weight gain in high-dose males still trailed controls by 9%, but was increased by 35% in high-dose females. High-dose males still had elevated relative spleen weights (127%), but no changes were noted during gross or microscopic examination of the spleen. The only lesion still evident in the animals was periportal hepatocyte vacuolation in 5/8 high-dose males, but the severity was decreased to minimal to mild. All remaining indicators of toxicity observed during treatment were generally comparable to controls or were not biologically significant following the recovery phase.

The LOAEL is 4.5 mg/kg/day (lowest dose tested) in male and female rats and is based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female. An NOAEL was not determined.

This subchronic toxicity study is classified as **Acceptable** and satisfied the OPPTS 870.3100 subchronic (90-Day) oral toxicity in rodents.

4.3 Reproductive and Developmental Toxicity

There were no submitted studies on reproductive toxicity of **BBAB**. There were two studies submitted to evaluate the developmental effects of BBAB :one range-finding developmental toxicity rat study and one definitive rat developmental study.

In the dose range-finding rat developmental toxicity study (MRID 44739401), maternal toxicity occurred in dams treated with 50 mg/kg/day and higher. Gross clinical examination revealed increased salivation and decreased body weights, body weight gains, and food consumption. Internal examination revealed gastric irritation (reddened mucosa, thickening, distention, fluid-filled, and/or dark red areas) and enlarged adrenals. Treatment with 50 mg/kg/day resulted in post-implantation loss accompanied by increases in the number of resorptions/dam (both early and late resorptions), and decreases in the number of live fetuses/litter, mean fetal body weights, and gravid uterine weights.

In the definitive developmental toxicity study (MRID 44750901), 25 bred Crl:CD®(SD)BR rats per group were administered **BBAB** (Lot/Batch No. K.D.D., 93.5% a.i.) in Mazola® corn oil orally by gavage at doses of 0, 5, 20, or 35 mg/kg/day on gestation days (GD) 6-19, inclusive. On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally, viscerally, and skeletally for malformations/variations.

One mid-dose female was found dead on GD 16 from gavage trauma. All other animals survived to scheduled necropsy. Maternal toxicity was manifested in the 20 and 35 mg/kg/day groups. During the treatment period of GD 6-20, dose-related, increased salivation prior to dosing correlated with observation of clear and tan matting around mouth at the time of dosing and 1-hour post-dosing in both the mid- and high-dose groups. The treatment related increased salivation was considered to be associated with the corrosivity of **BBAB**. In addition, the 35 mg/kg/day group also had statistically significant decreases in mean maternal absolute body weights, body weight gains, and food consumption. Mean absolute body weights were statistically significantly decreased ($p<0.05$; 0.01) starting on GD 12 and continuing to study termination on GD 20 (93% to 95% of controls). For the overall treatment period (GD 6-20), high-dose dams gained 20% less weight and consumed 9% less food than controls ($p<0.01$), and had final absolute and corrected body weights 7% and 8% less than controls, respectively ($p<0.01$).

No treatment-related differences in body weights, body weight gains, or food consumption were noted in low- or mid-dose dams. No treatment-related effects were noted in any of the treatment groups during gross necropsy.

Therefore, the maternal toxicity LOAEL is 20 mg/kg/day based on an increased incidence of salivation, and the maternal toxicity NOAEL is 5 mg/kg/day.

Mean fetal body weight was statistically significantly (p#0.05) decreased in the high-dose group (3.5 g) as compared with controls (3.7 g). No dose- or treatment-related, statistically significant effects on pregnancy rates, number of corpora lutea, pre- or post-implantation losses, resorption/dam, fetuses/litter, or fetal sex ratios were observed in the treated groups as compared with the controls. No dams had complete litter resorption.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any litter. Most treated and control litters contained fetuses with minor variations in skeletal ossification.

Therefore, the developmental toxicity LOAEL is 35 mg/kg/day based on decreased mean fetal body weights, and the developmental toxicity NOAEL is 20 mg/kg/day.

This developmental toxicity study is classified as **Acceptable/guideline** and fulfills the OPPTS 870.3700 Prenatal Developmental Toxicity Study Guideline.

4.4 Mutagenicity and Carcinogenecity

There were no data submitted for evaluating the carcinogenicity of **BBAB**. There were three studies submitted to study the mutagenic potential of **BBAB**. The results of these three studies are summarized in **Table 3**.

In the Ames test, with or without the microsomal activation (S-9 fraction), **BBAB** was not mutagenic to *Salmonella typhimurium* tester strains TA98,TA100, TA1535, and TA1537. In the mouse lymphoma assay, cultures of mouse lymphoma (L5178Y) cells were exposed to **BBAB** solutions for determination of potential to induce forward mutation at the thymidine kinase (TK+ to TK-) locus. Under S9 activation, a dose related increased frequency of mutant colonies occurred at a level of moderate toxicity. Without S-9 activation, however, **BBAB** was active at moderate to severe cytotoxicities. This effect was deemed "equivocal" because the mutagenic activity is only obvious in the presence of excessive toxicity (<10% of total growth); however a possible clastogenic effect was suggested. **BBAB** was negative for micronucleus induction in mice in the *in vivo* ICR Mouse Bone Marrow Micronucleus Test.

Table 3: Mutagenicity of 1,4 (bis) Bromoacetoxy-2-butene (BBAB)

MRID Number	Study type	Testing Strains/Animals	Dosage	Conclusion
432010-01	Reverse Gene Mutation - Ames Test (870.5265)	TA98,TA100, TA1535, and TA1537	100-333 µg/plate/-S9; 33-1000 µg/plate/ +S9	**BBAB** was negative in Ames test up to cytotoxic doses
4320260-1	Mutagenicity - in mammalian Cell Culture - in vitro (870.5300)	L5178/TK+ mouse Lymphoma Assay	0.5-3.0 µg/ ml (-S9) ; 5.0-30.0 µg/ml (+S9)	**BBAB** was positive in mouse lymphoma cell cultures under S9 activation, but "equivocal" in the absence of exogenous metabolic activation.
431563-01	Bone Marrow Micronucleus Test (870.5385)	ICR Mouse	34,68, and 135 mg/kg, IP	Negative for micronucleus induction in mice.

4.4 Neurotoxicity

There are no submitted neurotoxicity studies. However, signs of neurotoxicity were noted in following studies:

(1) In the subchronic toxicity study (MRID 44757001),10 Sprague-Dawley Crl:CD®(SD)IGS BR rats/sex/group were administered BBAB (Lot No. KDD, Batch # 9, 93.1% a.i.) in Mazola® corn oil orally by gavage at doses of 0, 4.5, 22.5, or 39.1 mg/kg/day for a minimum of 90 consecutive days. Clinical signs observed in surviving 22.5 and 39.1 mg/kg/day doses animals included a dose-related increase in salivation prior to and post dosing, and high-dose animals additionally had decreased activity and wobbly gait. The incidence rates and occurrence of decreased activity and wobbly gait were greater in males than females.

(2) In the range-finding prenatal developmental study (MRID 44739401), eight bred Crl:CD®(SD)BR rats per group were administered BBAB (Lot/Batch No. K.D.D., 93.5% a.i.) in Mazola® corn oil orally by gavage at doses of 0, 25, 50, 75, 100, or 150 mg/kg/day on gestation days (GD) 6-19, inclusive. Numerous signs were observed in animals dosed with 50 mg/kg/day and higher. Potential neurotoxic signs included hypoactivity; head held low; drooping/closed eyelid; body dragging, rocking, lurching or swaying while walking; flattened body/extended limbs; prostration; and abnormal respiration. Additionally, one or more 50 mg/kg/day group dams occasionally exhibited circling, splayed hindlimbs, walking on tiptoes, sporadic nasal clicks, hunched or unkempt appearance.

(3) In an acute dermal toxicity in rabbit with BBAB (MRID 43152401), necropsy examination revealed congested meningeal vessels in dead animals.

5.0 HAZARD ENDPOINT SELECTION

The doses and endpoints for short-term, intermediate-term and long-term occupational or residential exposure have been selected for **BBAB** by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC). For dietary risk assessment, because there are data gaps, a final dietary risk assessment for BBAB must be deferred , pending submission of the missing data. **Table 4** summarizes the toxicological dose and endpoints for **BBAB** for use in human risk assessments.

5.1 Acute Reference Dose (RfD)

Because there are data gaps, a final dietary risk assessment for BBAB must be deferred , pending submission of the missing data.

5.2 Chronic Dietary Reference Dose (RfD)

Because there are data gaps, a final dietary risk assessment for BBAB must be deferred , pending submission of the missing data.

5.3 Occupational/Residential Exposure

5.3.1 Dermal Absorption

Dermal Absorption Factor:

There is no appropriate dermal absorption study for **BBAB** available. Because the corrosivity of this chemical, 100% dermal absorption should be used in dermal risk assessment.

5.3.2 Short-Term Dermal - (1-7 Days)

Study Selected: 90-day oral (Gavage) study - Rat § OPPTS 870.3100

MRID No.: 44757001

Executive Summary:

In a subchronic toxicity study (MRID 44757001), 10 Sprague-Dawley Crl:CD® (SD)IGS BR rats/sex/group were administered **BBAB** (Lot No. KDD, Batch # 9, 93.1% a.i.) in Mazola® corn oil orally by gavage at doses of 0, 4.5, 22.5, or 39.1 mg/kg/day for a minimum of 90 consecutive days. An additional 10 animals/sex/group were incorporated into the control and high-dose groups for a recovery phase. The **LOAEL** is 4.5 mg/kg/day (lowest dose tested) in male and female rats and is based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female. A **NOAEL** was not determined

Dose/Endpoint for Risk Assessment:

The **LOAEL** is 4.5 mg/kg/day (lowest dose tested) in male and female rats and is based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female.

Comments about Study/Endpoint:

Because an NOAEL was not determined, an extra uncertainty factor of 3 should included. A margin of exposure (MOE) of 300 is required.

5.3.3 Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 90-day oral (Gavage) study - Rat § OPPTS 870.3100

MRID No.: 44757001

Executive Summary:

See short tern dermal above.

Dose/Endpoint for Risk Assessment:
The **LOAEL** is 4.5 mg/kg/day (lowest dose tested) in male and female rats and is based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female. An **NOAEL** was not determined

Comments about Study/Endpoint:
A MOE of 300 is required because of the use of a LOAEL. This risk assessment is required.

5.3.4 Long-Term Dermal (Several Months to Life-Time)

Study Selected: 90-day oral (Gavage) study - Rat § OPPTS 870.3100

MRID No.: 44757001

Executive Summary:
See short term dermal above.

Dose/Endpoint for Risk Assessment:
The **LOAEL** is 4.5 mg/kg/day (lowest dose tested) in male and female rats and is based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female. An **NOAEL** was not determined

Comments about Study/Endpoint:
A MOE of 300 ir required since a LOAEL is used. This risk assessment is required.

5.3.5 Inhalation Exposure (Any Time Period)

Due to the low vapor pressure (1.59×10^{-6} Torr at $20^{O}C$), inhalation exposure risk assessment is not required when evaluating the paper and oil industry uses of **BBAB**. However, for water-based paint use, when painting with a spraying system (e.g. sprayer), inhalation may be a potential exposure route. There is no inhalation study in the submitted database. In addition, route-to-route extrapolation is not considered to be appropriate for BBAB. The route to route exposure should only be used when the following conditions are met:

1. The considered effects are independent of the exposure route;
2. Absorption efficiency is the same among routes or differs by a known degree;
3. Half-life of the substance is long (exhibiting stable blood and/or tissue concentration);
4. First pass effects by the routes of concern are minimal;
5. There is no significant chemical transformation by intestinal flora; and
6. The chemical is relatively soluble in body fluid.

For, BBAB, the route to route extrapolation is not considered to be appropriate because:

1. There is no pharmacokinetic information available to determine the absorption efficiency, biological-half life and the biological distribution of the chemical in the system; and
2. The chemical is corrosive and first pass effects by route should not be considered to be minimal.

Therefore, **a 28-day inhalation study** is considered as a data gap and was suggested to minimize the uncertainties caused by the route to route (oral to inhalation) extrapolation. Therefore, the risk assessment associated with inhalation exposure for **BBAB** must be deferred , pending submission of the missing studies.

5.3.6 MOEs for Occupational/Residential Exposure Risk Assessments

A MOE of 300 is selected for short, intermediate, and long-term dermal risk assessments.

Table 4. Summary of Toxicological Dose and Endpoints for BBAB for Use in Human Risk Assessment (1,2)

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Short-Term, Intermediate-Term, and Long Term (Dermal)	LOAEL (3) = 4.5 MOE = 300	Based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female.	90-day Rat Gavage study MRID 44757001

Note:

(1). LOAEL = lowest observed adverse effect level, MOE = margin of exposure

(2). The toxicological endpoints for dietary and inhalation risk assessment for **BBAB** must be deferred , pending submission of the missing studies.

(3). The use of a 100% dermal absorption rate is required for dermal risk assessments.

6.0 FQPA CONSIDERATIONS

As discussed in the **Background Section**, for indirect food uses such as slimicide use, the minimum data set need to address the need for an FQPA risk assessment includes two subchronic oral toxicity studies (rodent and non-rodent), a multi-generation reproduction toxicity study, a developmental toxicity study, and a mutagenicity battery. For BBAB, the absence of a subchronic non-rodent study and one reproduction study precludes a determination on whether to retain the 10x FQPA safety factor.

7.0 REFERENCES

San, R.C. and Klug, J.J. (1994) Salmonella Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay. Microbiological Associates Inc. (MAI), Rockville, MD. Laboratory Study No.: (MAI) TE064.501014, April 6, 1994. MRID 43201001. Unpublished.

Putnan, D.C. And Young, R.R. (1994) Micronucleus Cytogenetic Assay in Mice. Microbiological Associates Inc. (MAI), Rockville, MD. Laboratory Study No.: (MAI) TE064.122. March 04, 1994. MRID 43156301. Unpublished.

San, R.C. and Clarke, J.J. (1994) L5178Y/TK$^{+/-}$ Mouse Lymphoma Mutagenesis Assay. Microbiological Associates Inc. (MAI), Rockville, MD. Laboratory Study No.: (MAI) TE064.702020, April 5, 1994. MRID 43202601. Unpublished.

Douds, D.A. (1994) An Acute Toxicity Study in Rats with BBAB. Springborn Laboratories (SLS), Spencerville, OH. Laboratory Study No.: SLS 3138.99, March 22, 1994. MRID 43181101. Unpublished

Douds, D.A. (1994) An Acute Dermal Toxicity Study in Rabbits with BBAB. Springborn Laboratories (SLS), Spencerville, OH. Laboratory Study No.: SLS 3138.100, February 28, 1994. MRID 43152401. Unpublished

Cappon, G. (1999) A dose range-finding prenatal developmental toxicity study of BBAB in rats. WIL Research Laboratories, Inc., 1407 George Road, Ashland, OH. Laboratory Study No.: WIL-94051, January 14, 1999. MRID 44739401. Unpublished.

Cappon, G. (1999) A prenatal developmental toxicity study of BBAB in rats. WIL Research Laboratories, Inc., 1407 George Road, Ashland, OH. Laboratory Study No.: WIL-94052, January 14, 1999. MRID 44750901. Unpublished.

Rush, R. (1999). A 90-day oral (gavage) toxicity study in rats with a 28-day recovery phase. Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH. SLI Study No. 3138.109, January 25, 1999. MRID 44757001. Unpublished.